

## REMARKS

Claims 1, 4, 6, 10 and 13-18 are pending in this application. Applicants have amended claims 10 and 13-18 in the instant paper.

The Examiner made the following rejection in the non-final Office Action mailed December 31, 2007:

- 1) The Examiner rejects claims 1, 4, 6, 10 and 13-18 under 35 U.S.C. §103(a) over WO 99/30561 to Warren in view of Holmes (Expert Opinion on Investigational Drugs, 2001), Apelgren *et al.* (Cancer Research, 1990) and U.S. Patent 5,997,861 to Virtanen *et al.*

Applicants believe the following amendments and remarks traverse the Examiner's pending rejection.

### **1. The Claims Are Not Obvious**

The Examiner maintains the rejection of claims 1, 4, 6, 10 and 13-18, under 35 U.S.C. §103(a), as being allegedly unpatentable over Warren in view of Holmes (of record), Apelgren *et al.* (of record) and Virtanen *et al.* (of record). In the previous office action, the Examiner alleged a proper evaluation of obviousness, as set out in *Graham v. Deere*, had been applied to the pending claims in view of the cited art.<sup>1</sup> Furthermore, the Examiner alleged that Holmes (while silent on aptamers) nonetheless motivates one skilled in the art to produce conjugates comprising aptamers targeted to PSMA.<sup>2</sup> Applicants disagree.

Applicants submit that without the benefit of their application as a road map, one of ordinary skill in the art would not have been able to recapitulate the claimed embodiments of the present invention at the time it was filed. Significantly, the Federal Circuit recently held that "in cases involving new compositions of matter, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda v. Alphapharm*, 492 F.3d, 1350, 1357, CAFC (2007).

The Examiner alleges that Holmes and Warren motivate one skilled in the art to produce conjugates comprising aptamers targeted to PSMA. More specifically the Examiner alleges,

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<sup>1</sup> Office Action dated March 27, 2007, p. 3.

“[t]he Holmes reference provides a motivation to target PSMA therapeutically by teaching that the protein is preferentially expressed in prostate tissue and express at increased level in cancerous cells. The motivation to use an aptamer to target a drug comes from the Warren reference.”<sup>3</sup>

Applicants respectfully disagree. Holmes teaches that antibodies may be raised against a protein (*i.e.* PSMA) expressed by prostatic epithelial cells. Warren, on the other hand, teaches the use of nucleotide based *prodrugs* and the delivery of the same. Warren defines a “prodrug” as “a compound that exhibits pharmacological activity after undergoing a chemical transformation in the body.”<sup>4</sup>

In contrast, the pending claims describe aptamer-toxin conjugates. Applicants define “aptamer-toxin conjugates” as “molecules that have lethal or growth inhibiting effects on cells.”<sup>5</sup>

Furthermore, applicants teach that,

“[t]he nucleic acid moiety binds to a desired cell or cell surface marker. The linked cytotoxic agent is thus brought in close proximity of the cell, which allows for the cytotoxic agent to exert its cytotoxic effects on the cell.”<sup>6</sup>

In this respect, the claimed embodiments of the present invention rely on the native toxicity of the cytotoxic moiety of the aptamer-toxin conjugate to act directly on the targeted cell. Warren cannot provide the reason, as required by the *Takeda* Court, to design an anti-PSMA aptamer to deliver an active cytotoxic agent to a PSMA expressing cell because Warren teaches the delivery of inactive *prodrugs* to a tissue compartment. By definition, the prodrugs in Warren cannot be considered a cytotoxic moieties because these prodrugs require some post-administration “chemical transformation” to become therapeutic. Therefore, applicants respectfully request that the claim rejections under 35 U.S.C. § 103(a) be withdrawn.

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<sup>2</sup> *Id.*

<sup>3</sup> Office Action dated December 31, 2008, p. 5.

<sup>4</sup> WO 99/30561, p. 26.

<sup>5</sup> U.S. Patent Application No. 10/826,077, paragraph [0011].

<sup>6</sup> *Id.* at paragraph [0059].

## CONCLUSION

Applicants submit the amendments and arguments set forth above traverse the Examiner's rejections and, therefore, request these rejections be withdrawn and the pending claims be passed to allowance. Should the Examiner believe a telephone interview would aid in the prosecution of this application, applicants encourage the Examiner to call the undersigned collect at 617.542.6000.

Respectfully submitted,

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